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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/539,382	03/31/2000	Alison A. McCormick	LSB-001/CIP	9680

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VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/539,382	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14 & 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The examiner of the application has changed. This case has now been transferred as of 11/18/02. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

Continued Prosecution Application

2. The request filed on 6/21/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/539,382 is **acceptable** and a CPA has been established. An action on the CPA follows.

3. The amendment filed 7/21/02 (paper no. 13) is acknowledged and entered into the record. Accordingly, claims 1-53 are canceled and replaced with new claims 54-76. Therefore, claims 54-7 are pending and examined on the record.

Information Disclosure Statement

4. The Information Disclosure Statements filed 6/21/02 & 8/8/02 (paper nos. 14 &16) are acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

6. Claims 54-76 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a polynucleotide sequence that reads on nucleotide sequences that could be found in nature. As such the invention lacks the hand of man.

Claim Rejections - 35 USC § 112 – 35 USC 112, 2nd paragraph

7. Claims 54-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Regarding claims 66 and 76 in the recitation of the term "about", it is unclear as to the number of amino acids claimed, the amount administered, and the intervals of time. The term "about" is a relative term and as such renders the claim indefinite, because one of skill in the art would not know whether it is 48,49, 51, or 52 amino acids, 15 or 50 mg, and 7, 12, or 14 days.

Claim Rejections - 35 USC § 112 – 35 USC 112, 1st paragraph

9. Claims 54-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide that encodes a scFv, that is useful in the treatment of B-cell lymphomas, wherein the B-cells express an Ig on the surface of the cell, wherein the polypeptide is produced in a plant does not reasonably provide enablement for a nucleotide that encodes any polypeptide self antigen useful as a vaccine to treat any tumor or any patient at risk of developing a tumor, wherein the B-cell expresses any epitope, and wherein the polypeptide is produced in any cell or organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using

it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are drawn to a polynucleotide that encodes a polypeptide self-antigen that is useful as a vaccine to treat a tumor, wherein the polypeptide is an epitope expressed on a tumor, and the polypeptide is produced by a cell or organism that has been transformed with a nucleotide sequence derived from a tumor of a subject.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that B-cell lymphomas express Ig molecules on the surface of the cell. These Ig molecules can be utilized as potential B-cell tumor markers, and as such, anti-idiotypic antibodies that are either whole antibodies or antibody fragments that recognize idiotypes on the surface expressed Ig molecules can used as an antigen, eliciting the immune response against the B-cells expressing such Ig molecules on their surfaces (see Casper *et al* (Blood 1997; 90(9):3699-3706) and McCormick *et al* (PNAS USA 1999;96:703-708)). The art also teaches that products, that are intended as cancer vaccines, are challenging and perhaps impossible wherein the "notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction." (Evans *et al* Q J Med 1999; 92:299-307, see page 303).

The amount of direction or guidance present and the presence or absence of working examples: The instant specification has taught the isolation of polynucleotide sequences encoding VH and VL regions of a surface expressed Ig molecule from bone marrow aspirates by RT-PCR. The specification also discloses the generation of a polynucleotide sequence encoding an scFv to be used as an antigen to elicit a polyclonal antibody immune response for the treatment of B-cell lymphomas. Furthermore, the specification has only taught the successful expression of such scFv through the recombinant production using a plant system. However, the specification is limited in its teachings of a polynucleotide that encodes anything other than scFv and is limited in the teachings of this product as a vaccine or to be administered to one at risk of developing a tumor. Furthermore, the polynucleotide sequence encoding

polypeptides self antigens useful as claimed has not been adequately taught to be used for the treatment of any other type of cancer other than to treat B-cell lymphomas, which express an Ig epitope. As a result, one of skill in the art would not be able to practice the invention to fulfill all the limitations set forth in the claim, because the specification has not fully taught how to use the polynucleotide commensurate in scope to the claims. For example, the specification has only taught a polynucleotide that encodes an scFv, which is one type of epitope found on the surface of a specific type of tumor, namely, a B-cell lymphoma. The specification has also not taught any vaccine or method of treating any subject at risk of developing a tumor because it is difficult to determine the population that would be at risk of developing a tumor or cancer, because one of skill would not know who would be predisposed to developing tumors. Furthermore, as pointed out in the specification, the expression of the polynucleotide encoding a self antigen (scFv) that is capable of correctly folding is problematic in expression system other than a plant expression system because of the folding and secretion problems. As such, one of skill in the art would not know how to practice or make the invention commensurate in scope to the claims because any expression system is claimed for making a polypeptide encoded for by a polynucleotide, of which only plants are enabled and taught. Therefore, given the reasoning above, one of skill in the art is only able to make a polynucleotide encoding an scFv in a plant recombinant expression system to be used in treating B-cell lymphomas as an antigen to stimulate the immune system to react against an Ig molecule epitope expressed on the surface of a B-cell lymphoma.

The breadth of the claims and the quantity of experimentation needed: Given the broad range of peptides, tumors, expression systems, encompassed within the claims, which includes any tumor associated peptide, any tumor type of which there is a tumor associated antigen, and any expression system that can make polypeptides, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 54, 57-66, 70, 72-73, and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Casper *et al* (Blood 1997 Nov; 90(9):3699-3706). Claims are drawn to a polynucleotide sequence that encodes a polypeptide self antigen useful as a tumor specific vaccine in a subject with a tumor or in a subject at risk of developing a tumor, wherein: (1) the epitope is unique to or over expressed by the tumor cells, (2) the polypeptide is produced in a cell or organism transformed by the nucleic acid, (3) the polypeptide is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide is capable of inducing an immune response. The claims are further drawn to a polynucleotide wherein the polypeptide has at least two peptide domains, wherein said tumor is a B-cell lymphoma and said epitope is a surface Ig

epitope, wherein said polypeptide comprises at least one idiotypic epitope of the V region of said surface Ig, wherein there are at least two V regions of which at least part of the VH and VL are also domains of the said Ig, wherein the VH region has a CDR of which it is specifically CDR2, wherein the polypeptide is a two domain scFv that includes and or comprises VH and VL domains, wherein the polypeptide is linked by a linker, which is a member of a randomized library of linkers of which the first and second nucleotide is selected from dA, dG, dC, or dT wherein the polypeptide is in solution, the immune response is a protective anti-tumor immune response, and wherein the antibody response is measured by an enzyme immunoassay or by flow cytometry.

Casper *et al* (Blood 1997 Nov 1; 90(9):3699-3706) teach the use of an idiotypic vaccine for the treatment of B-cell lymphoma, wherein the idiotypic vaccine recognizes a tumor derived idiotype that is a surface Ig molecule. Casper *et al* further teach the production of the polypeptide in a cell which was transformed by a nucleotide sequence that encoded the polypeptide, which was able to induce an immune response, that is in the absence of evidence to the contrary presumed to be correctly folded. Casper *et al* also teach a polypeptide that has at least two domains of at least one idiotypic epitope and comprises at least two V regions of which are VH and VL that are a part of a VH and VL of the surface Ig molecule. The VH regions, in the absence of evidence to the contrary includes at least one CDR of which is CDR2. In addition, Casper *et al* also teach that the polypeptide is a two domain scFv that comprises VH and VL that is linked by a randomized linker. Finally, Casper *et al* also teach that the administration of scFv

in a PBS solution that was able to elicit an immune response in the attempt to have an anti-tumor response, wherein the immune response is measured by an ELISA.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 54-67, 70, 72-73, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casper *et al* in view of McCormick *et al* (PNAS USA 1999 Jan; 96:703-708). The claims are drawn to a polynucleotide that is disclosed in paragraph 10 of the instant office action, but further limited to a polynucleotide that encodes a polypeptide that is transiently produced in a plant.

Casper *et al* (see paragraph 10 of the instant office action for Casper *et al* disclosure) fails to disclose the production of the polypeptide in a plant and also fails to particularly teach transient expression of the polypeptide. However, McCormick *et al* teach that a scFv derived from a tumor that is expressed in a plant could be used for idiotypic treatment of lymphomas.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize a polynucleotide that encoded a polypeptide that was an scFv derived from a surface expressed Ig molecule and transiently produced in a plant because Casper *et al* teach that basic premises of utilizing a polynucleotide that encoded an scFv for the treatment of a B-cell lymphoma by utilizing an epitope located

on the surface of the B-cell lymphoma and making a vaccine that contained idiotypes to that surface expressed Ig molecule. In addition, the McCormick suggests that the production of transiently produced protein in the plant system has many advantages over other recombinant systems of protein production. One of skill in the art would have been motivated to produce the scFv in a plant because of proper folding of the protein following isolation of the protein from the cellular expression system. Furthermore, the production of the protein via transient expression is more adventagous over stable expression because the turn around times are faster. Further still, McCormick discloses that other scFv have been produced using the plant system and that such scFv have been successful in reacting as anti-idiotypic antibodies in solution. One of skill would have expected a great deal of success in trying the method taught by McCormick because they have already shown that other scFv were soluble, capable of being secreted, and reactive.

14. Claims 54, 57-67, 70, 72-73, and 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casper *et al* in view of King *et al* (Nature Med 1998 Nov;4(11):1281-1286).

Casper *et al* (see paragraph 10 of the instant office action for Casper *et al* disclosure) fails to disclose the process of administration of the scFv polypeptide encoded by the corresponding polynucleotide, wherein the administration of about 15 ug of polypeptide is administered three time about three weeks apart. However, King *et al* teach that an scFv polypeptide is administered at about 15 μg subcutaneously, wherein the administration of the polypeptide is given about two weeks apart.

It would have been *prima facie* obvious to one of ordinary skill in the art to administer the scFv polypeptide encoded for by the polynucleotide as taught by Casper *et al* through the subcutaneous route because King *et al* teaches that such administration is possible and that such administration was able to achieve an immune response to an epitope on the surface of a B-cell lymphoma. One of ordinary skill in the art would have been motivated to administer the scFv polypeptide encoded for by a polynucleotide because King *et al* taught the method of administration and provided dosage and administration intervals, and Casper *et al* taught the scfV polypeptide encoded by a polynucleotide. One of ordinary skill would have had a reasonable expectation of success in administering the polypeptide because the dosages and time intervals disclosed by King *et al* also should an effective immune response.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
November 26, 2002